

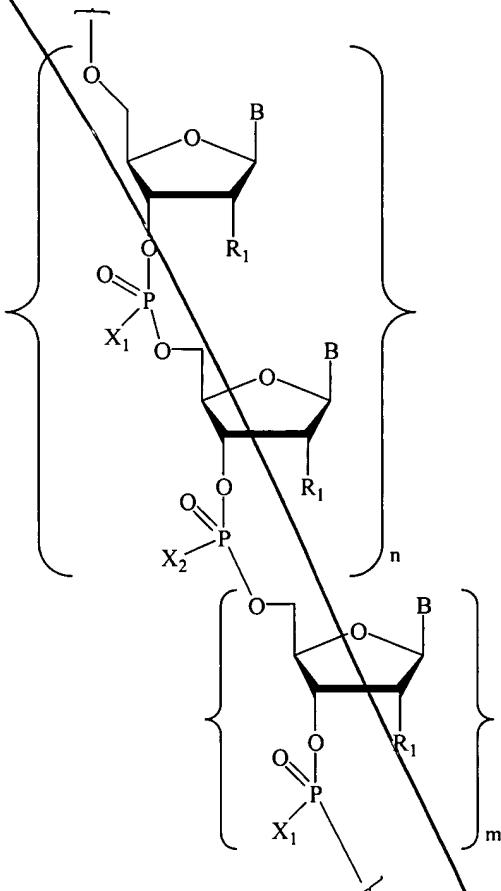
*same base composition

In the claims:

Please cancel claims 1-27 and 31-33.

Please rewrite claims 28-30 as follows.

28. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:



wherein:

Sub B

each B is a nucleobase;

one of X₁ or X₂ is O, and the other of X₁ or X₂ is S;

each R₁ is, independently, H, hydroxyl, C₁-C₂₀ alkyl, C₃-C₂₀ alkenyl, C₂-C₂₀ alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

A5 copied

or R₁ is a group of formula Z-R₂₂-(R₂₃)_v;

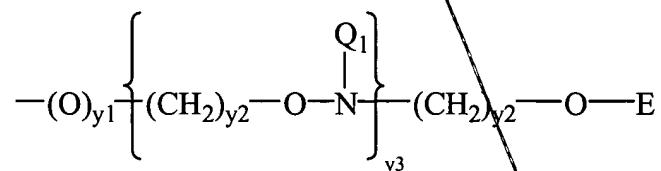
Z is O, S, NH, or N-R₂₂-(R₂₃)_v;

R₂₂ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, or C₂-C₂₀ alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R₁ has the formula:



wherein:

y₁ is 0 or 1;

y₂ is independently 0 to 10;

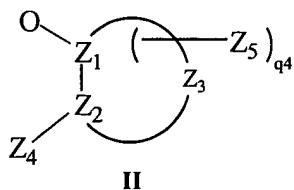
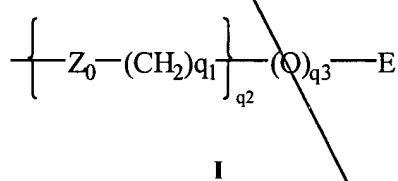
y₃ is 1 to 10;

E is C₁-C₁₀ alkyl, N(Q₁)(Q₂) or N=C(Q₁)(Q₂);

each Q₁ and Q₂ is, independently, H, C₁-C₁₀ alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q₁ and Q₂, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

A5 cont'd

or R₁ has one of formula I or II:



B1
wherein:

Z₀ is O, S, or NH;

q¹ is from 0 to 10;

q² is from 1 to 10;

q³ is 0 or 1;

q⁴ is, 0, 1 or 2;

Z₄ is OM₁, SM₁, or N(M₁)₂;

each M₁ is, independently, H, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C(=NH)N(H)M₂, C(=O)N(H)M₂ or OC(=O)N(H)M₂;

M₂ is H or C₁-C₈ alkyl;

Z₁, Z₂ and Z₃ comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Sub B

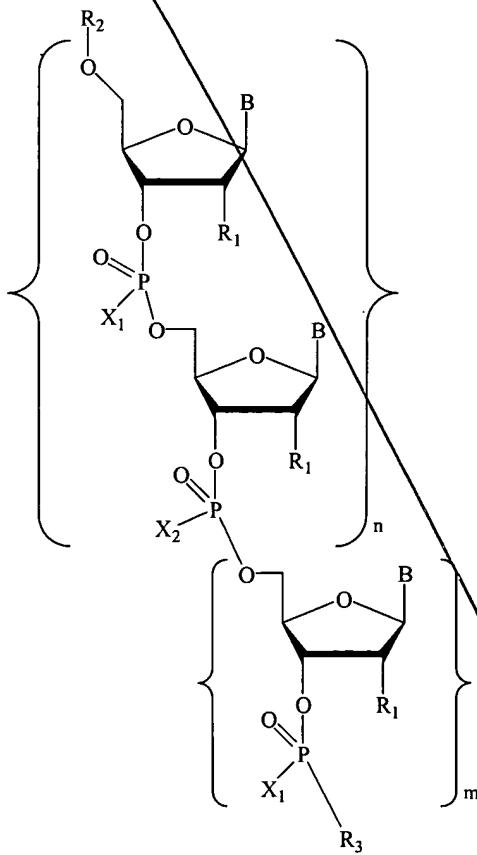
~~Z_s is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(Q₁)(Q₂), OQ₁, halo, SQ₁ or CN;~~

~~n is from 2 to 50; and~~

~~m is 0 or 1.~~

AS signed

~~29. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:~~



wherein:

each B is a nucleobase;

Sub B

X₁ is S;

X₂ is O;

each R₁ is, independently, H, hydroxyl, C₁-C₂₀ alkyl, C₃-C₂₀ alkenyl, C₂-C₂₀ alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

Recd

or R₁ is a group of formula Z-R₂₂-(R₂₃)_v;

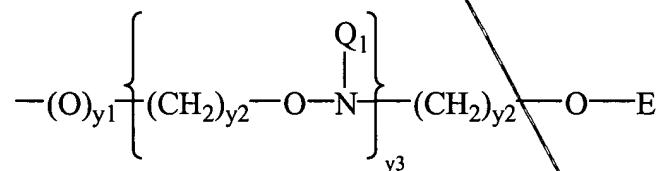
Z is O, S, NH, or N-R₂₂-(R₂₃)_v;

R₂₂ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, or C₂-C₂₀ alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R₁ has the formula:



y1 is 0 or 1;

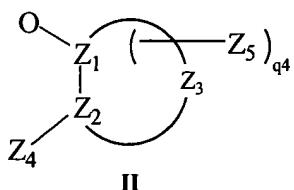
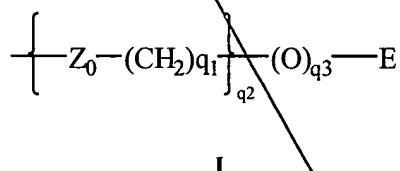
y2 is independently 0 to 10;

y₃ is 1 to 10;

E is C₁-C₁₀ alkyl, N(Q₁)(Q₂) or N=C(Q₁)(Q₂);

each Q₁ and Q₂ is, independently, H, C₁-C₁₀ alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q₁ and Q₂, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R₁ has one of formula I or II:



wherein:

Z₀ is O, S, or NH;

q¹ is from 0 to 10;

q² is from 1 to 10;

q³ is 0 or 1;

q⁴ is, 0, 1 or 2;

Z₄ is OM₁, SM₁, or N(M₁)₂;

each M₁ is, independently, H, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C(=NH)N(H)M₂, C(=O)N(H)M₂ or OC(=O)N(H)M₂;

M₂ is H or C₁-C₈ alkyl;

Z₁, Z₂ and Z₃ comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z₅ is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to

about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(Q₁)(Q₂), OQ₁, halo, SQ₁ or CN;

n is from 2 to 50; and

m is 0 or 1;

R₂ is H, a hydroxyl protecting group, or an oligonucleotide; and

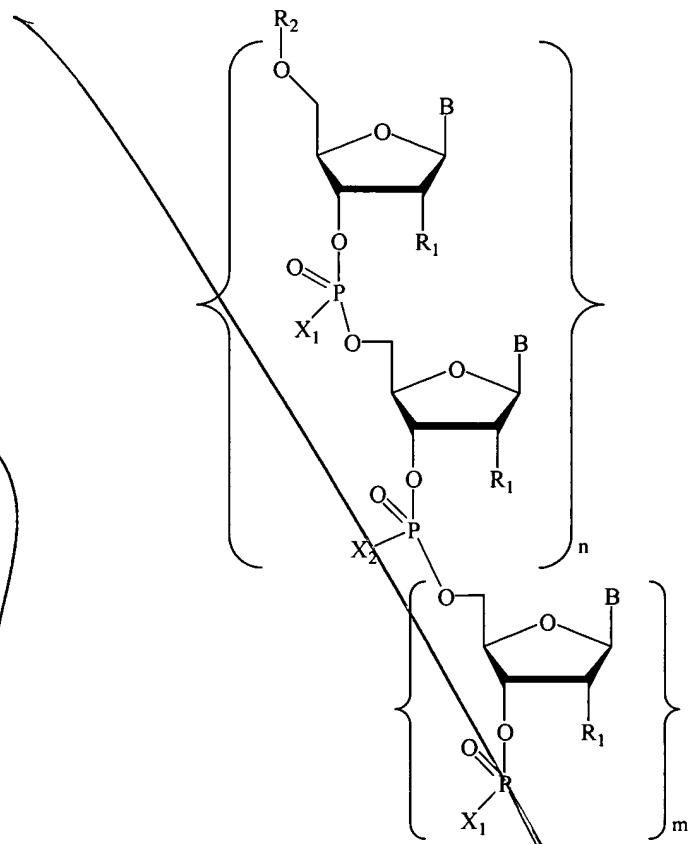
R₃ is OH, an oligonucleotide, or a linker connected to a solid support.

30. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:

(5') W¹-W²-W³ (3')

wherein:

W¹ has the Formula:



wherein:

each B is a nucleobase;

one of X₁ or X₂ is O, and the other of X₁ or X₂ is S;

each R₁ is, independently, H, hydroxyl, C₁-C₂₀ alkyl, C₃-C₂₀ alkenyl, C₂-C₂₀ alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R₁ is a group of formula Z-R₂₂-(R₂₃)_v;

Received

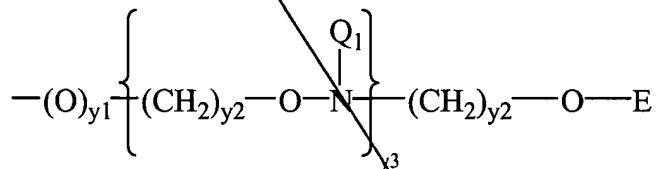
Z is O, S, NH, or N-R₂₂-(R₂₃)_v;

R₂₂ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, or C₂-C₂₀ alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, poly-alkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R₁ has the formula:



y₁ is 0 or 1;

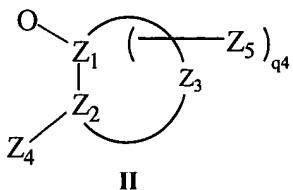
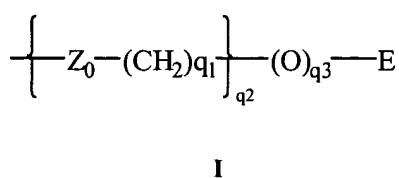
y₂ is independently 0 to 10;

y₃ is 1 to 10;

E is C₁-C₁₀ alkyl, N(Q₁)(Q₂) or N=C(Q₁)(Q₂);

each Q₁ and Q₂ is, independently, H, C₁-C₁₀ alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q₁ and Q₂, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R₁ has one of formula I or II:



SuB
A second

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1 , SM_1 , or $N(M_1)_2$;

each M_1 is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, $C(=NH)N(H)M_2$,

$C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1 - C_8 alkyl;

Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

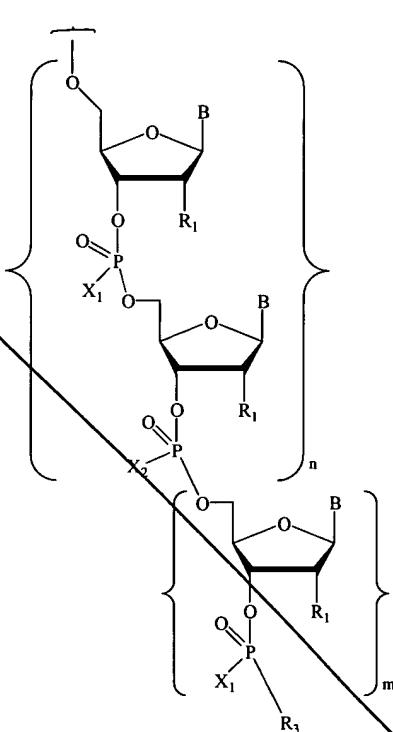
Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1 , halo, SQ_1 or CN ;

n is from 2 to 50; and

m is 0 or 1;

R_2 is H, a hydroxyl protecting group, or an oligonucleotide;

W^3 has the Formula:



wherein R_3 is OH, an oligonucleotide, or a linker connected to a solid support; and

W^2 is a plurality of covalently bound nucleosides linked by phosphodiester or phosphorothioate linkages.

Please add new claims 34-51 as follows.

34. (new) The method of claim 28 wherein R_1 is $-O-CH_2-CH_2-O-CH_3$.

35. (new) The method of claim 28 wherein n is about 5 to about 50.

36. (new) The method of claim 28 wherein n is about 8 to about 30.

37. (new) The method of claim 28 wherein n is about 4 to about 15.

38. (new) The method of claim 28 wherein n is 2 to about 10.
39. (new) The method of claim 29 wherein R₁ is -O-CH₂-CH₂-O-CH₃.
40. (new) The method of claim 29 wherein R₂ is H, and R₃ is OH.
- A continuation*
41. (new) The method of claim 29 wherein R₂ is a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.
42. (new) The method of claim 29 wherein R₃ is a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.
43. (new) The method of claim 29 R₂ and R₃ are each a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.
44. (new) The method of claim 30 wherein R₁ is -O-CH₂-CH₂-O-CH₃.
45. (new) The method of claim 30 wherein R₂ is H, and R₃ is OH.
46. (new) The method of claim 30 wherein n is about 5 to about 50.
47. (new) The method of claim 30 wherein n is about 8 to about 30.
48. (new) The method of claim 30 wherein n is about 4 to about 15.
49. (new) The method of claim 30 wherein n is 2 to about 10.

50. (new) The method of claim 30 wherein W² is a plurality of covalently bound nucleosides linked by phosphodiester linkages.

51. (new) The method of claim 30 wherein W² is a plurality of covalently bound nucleosides linked by phosphorothioate linkages.

REMARKS

Claims 28-30 and 34-51 are pending in this application.

Claims 1-27 and 31-33 have been canceled.

Claims 28-30 have been amended. Support for the amendments can be found, for example, in the original claims and throughout the specification. No new matter has been added.

Claims 34-51 have been added. Support for the added claims can be found, for example, in the original claims and throughout the specification. No new matter has been added.

Applicants believe that the claims presently before the Examiner patentably define the invention over the applied art and are otherwise in condition for ready allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"